Remarks

Applicants' amendments herein are made in compliance with certain requirements set forth in a previous Office Action or are made to present the rejected claims in a better form for consideration on appeal and entry thereof is respectfully requested.

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 3-7, 16-18, 30-35, 38-41, 43, 46-50, 66, 69, 71-74, 77 and 83-86 are pending in the application, with claims 1, 66 and 78 being the independent claims. Claims 9, 10, 11-14, 15,19-22, 42, 44, 45, 67, 70, 79, 80 and 81 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Applicants reserve the right to pursue the subject matter of the canceled claims in related applications. These amendments are believed to place the claims in condition for allowance. Support for the foregoing amendments may be found in the specification as well as in the claims as filed. The amendments do not raise new issues or require further search by the Examiner. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Interview

Applicants thank Examiner Wilson for the courteous and helpful interview extended to Carl Wheeler and Elizabeth Haanes on June 27, 2002. These amendments and remarks reflect the issues discussed at the interview.

Election/Restriction

The Examiner has made the restriction requirement final. Accordingly, claims 11-14 and 19-22 have been canceled. Applicants have amended the claims to recite delivery of Interferon α, thereby rendering the species election moot. Applicants reserve the right to pursue the canceled claims, as well as generic embodiments, in related applications.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 3-7, 9, 10, 15-18, 30-35, 38-50, 66, 67, 69-74, 77-81 and 83-86 remain rejected in the Office Action under 35 U.S.C. § 112, first paragraph as allegedly not enabled over the full scope, for reasons of record. Applicants understand the alleged enablement issues to relate to the type of DNA, regulatory regions (*e.g.* a promoter), the tissue of administration, active fragments of interferon α, cell- tissue- or tumor-specific expression of IFN-α, and combination therapy with other cytokines. Not in acquiescence to the rejection, but rather solely to advance prosecution, Applicants have canceled claims 7, 9, 10, 15, 42, 44, 45, 67, 70, 79 and 80. Applicants have also amended claim 1 to recite administration of a DNA plasmid encoding IFN-α or an active fragment thereof, through operable association with a promoter. Claim 7 has been amended to recite administration to skeletal muscle. Claims 66 and 78 have been amended to recite administration of a DNA plasmid encoding IFN-α or an active fragment thereof to the peritoneal cavity, and transfection in claim 78 need not be selective. Claims to combination therapy have been canceled. Claims 3, 7, 35, 38, 39, 43, 47-49, 69, 71-74, 83, 84 and 86 have been amended to appropriately depend from claims 1, 66 and 78.

With respect to "active fragments of IFN-α," Applicants respectfully disagree. Applicants have previously argued that there is clear guidance on the nature of an active fragment of IFN-α. Enabling support in the specification includes: (1) that an *active fragment* of IFN-α is defined as a fragment of the cytokine that displays the antiproliferative activity of the mature or full length cytokine (page 32, lines 22-23), (2) that assays for screening antiproliferative activity are disclosed (and additional assays are routine), and (3) that methods of making the fragments are disclosed and are also routine. Therefore, one of ordinary skill in the art could easily make and screen fragments for activity using only routine experimentation. Furthermore, *active fragments of hIFN-α* are disclosed in the specification, *e.g.*, polypeptides comprising amino acids 83-166 of SEQ ID NO:10, amino acids 61-166 of SEQ ID NO:10, amino acids 41-166 of SEQ ID NO:10, and amino acids 21-166 of SEQ ID NO:10 (page 33, lines 1-5).

In contradiction to the assertion of the Examiner, and to further support the Applicants position that it would not require undue experimentation for one of ordinary skill in the art to determine *active fragments* of IFN-α, Applicants point out that *active fragments* of IFN-α *were* known in the art at the time of filing. Freze *et al.* (*Biochem. Mol. Biol. Int. 33*:969-979 (1994) (Exhibit A)) report that a synthetic peptide corresponding to human interferon alpha-2 amino acid sequence 124-138 inhibits proliferation of T-lymphocytes *in vitro* (Page 969). Furthermore, Kontsek *et al.* (*Immunol. Letters 35*:281-284 (1993) (Exhibit B)) report that "[t]he binding sites of the mAbs were mapped using a set of synthetic peptides that covered the amino acid sequence of two predicted biologically active segments in the regions 31-53 and 63-85 of IFN-α2. We measured the capacity of fragments to inhibit the IFN-neutralizing activity of mAbs and located three linear epitopes around residues 42-

53, 63-76 and 77-85 of the IFN-α2 molecule." (Page 281, first column). When aligned with the sequence of SEQ ID NO:10, the biologically active regions disclosed *supra* are highly homologous to identical regions of SEQ ID NO:10 and furthermore, comprise the active fragment disclosed as amino acids 41-166 of SEQ ID NO:10 and the active fragment disclosed as amino acids 61-166 of SEQ ID NO:10.

Further, the Examiner states that, "[i]n addition, a fragment having antiproliferative activity is not equivalent to a fragment capable of treating cancer. A fragment merely having "antiproliferative activity" in an assay may simply slow cell growth but not be capable of treating cancer in a patient." (Paper No. 16, page 9). Applicants respectfully disagree. Fenton and Longo ("Cell Biology of Cancer," in *Principles of Internal Medicine*, Fauci *et al.*, eds. McGraw-Hill, New York, NY, p. 505 (1998) (Exhibit C)) explain that "[t]wo characteristic features define a cancer: cell growth not regulated by external signals (i.e., autonomous) and the capacity to invade tissues and metastasize to and colonize distant sites.... The first of these features, the uncontrolled growth of abnormal cells, is a property of all neoplasms, or new growths." *id.* It follows then that a treatment for cancer necessitates an agent which has antiproliferative activity. Blocking uncontrolled proliferation is the goal of other anti-cancer therapies such as radiation and chemotherapy. As outlined *supra, active fragments* of IFN-α are fully enabled in the specification, and were known in the art at the time of filing. As such, one of ordinary skill in the art would not need to perform any undue experimentation to determine additional fragments of IFN-α capable of treating cancer or metastases. Accordingly, Applicants respectfully request reconsideration of the rejection and further that it be removed.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 3-7, 9, 10, 15-18, 30-35, 38-50, 66, 67, 69-74, 77-81 and 83-86 remain rejected in the Office Action under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner asserts that claim 3 is unclear as whether control elements include both a promoter and polyadenylation signal. Further, the Examiner states that claim 43 is unclear as to the meaning of "region regulating gene expression," and that claims 44 and 45 are unclear as to the metes and bounds of "cell- and tissue-specific" cannot be determined. Finally, the Examiner points out that claims 71-74 and 83-86 are unclear as "construct" or "polynucleotide construct" lacks antecedent basis in parent claims 66 and 78, respectively. Paper No. 16 at page 13. It is not clear in this Office Action or the previous Office Action (Paper No. 13) why the Examiner has included claims 1, 4-7, 9, 10, 15-18, 30-35, 38-42, 46-50, 66, 67, 69, 70, and 77-81 in the present rejection. Clarification is respectfully requested.

Not in acquiescence to the rejection, but rather solely to advance prosecution, Applicants have canceled claims 44 and 45. Applicants have also amended claim 3 to recite a DNA plasmid *further* comprising a polyadenylation signal and transcription termination signal (i.e., in addition to a promoter). Similarly, claim 43 has been amended to recite a DNA plasmid *further* comprising a region regulating expression operably associated with the polynucleotide. Lastly, Applicants thank the Examiner for pointing out the clerical error in claims 71-74 and 83-86. These claims have been amended to appropriately depend from claims 66 and 78. In view of these amendments, Applicants respectfully request reconsideration of the rejection and further that it be removed.

Other Matters

In the June 27 interview, the Examiner requested that Applicants submit co-pending applications for review by the Examiner. An Information Disclosure Statement is attached hereto. This Amendment and Reply is being filed as a Request for Continuing Examination under 37 C.F.R. § 1.114 solely to allow entry of this IDS into the record.

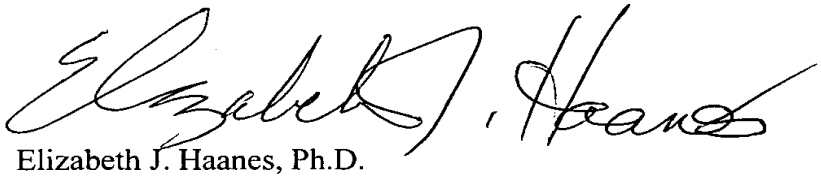
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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Version with markings to show changes made

In the Claims:

Claims 9, 10, 11-14, 15, 19-22, 42, 44, 45, 67, 70, 79, 80 and 81 were canceled.

The following claim 1 was substituted for the pending claim 1:

1. (Once Amended) A method of treating cancer or metastasis thereof in a mammal, comprising:

administering into a muscle of [said] a mammal a [non-infectious, non-integrating] DNA plasmid comprising a polynucleotide which encodes interferon-alpha [encoding a cytokine] or an active fragment thereof, through operable association with [one or more transcription control elements] a promoter; [, wherein said one or more transcription control elements comprises a promoter; and]

wherein said DNA plasmid is administered free from *ex vivo* cells;

[such that the cytokine encoded by said DNA polynucleotide] wherein said interferon alpha is expressed *in vivo*, and

[such that said cytokine] is present in the blood stream of said mammal in an amount effective to treat said cancer, or metastasis thereof.

The following claim 3 was substituted for the pending claim 3:

3. (Once Amended) The method of claim 1, wherein said [one or more transcription control elements] plasmid further comprises a polyadenylation signal and transcription termination signal in operable association with said polynucleotide.

The following claim 7 was substituted for the pending claim 7:

7. The method of claim 1, wherein said muscle tissue is [selected from the group consisting of] skeletal muscle[, smooth muscle, or myocardium].

The following claim 35 was substituted for the pending claim 35:

35. (Once Amended) The method of claim 1, wherein said DNA plasmid is dissolved in an aqueous solution.

The following claim 38 was substituted for the pending claim 38:

38. (Once Amended) The method of claim 1, wherein said DNA plasmid is administered free from association with transfection-facilitating proteins, viral particles, liposomes, cationic lipids, and calcium phosphate precipitating agents.

The following claim 39 was substituted for the pending claim 39:

39. The method of claim 1, wherein said DNA plasmid is administered as a complex of said DNA plasmid and one or more cationic compounds selected from the group consisting of cationic lipids, cationic peptides, cationic proteins, cationic polymers other than lipids or peptides, and mixtures thereof.

The following claim 43 was substituted for the pending claim 43:

43. (Once Amended) The method of claim 1, wherein said DNA plasmid further comprises a region regulating [gene] expression operably associated with said polynucleotide.

The following claim 47 was substituted for the pending claim 47:

47. (Once Amended) The method of claim 46, wherein said DNA plasmid is administered prior to the commencement of said one or more additional cancer treatment methods.

The following claim 48 was substituted for the pending claim 48:

48. (Once Amended) The method of claim 46, wherein said DNA plasmid is administered during the practice of said one or more additional cancer treatment methods.

The following claim 49 was substituted for the pending claim 49:

49. (Once Amended) The method of claim 46, wherein said DNA plasmid is administered after the end of said one or more additional cancer treatment methods.

The following claim 66 was substituted for the pending claim 66:

66. (Once Amended) A method of treating cancer in a mammal, comprising: administering into [a body] the peritoneal cavity of said mammal a [non-infectious, non-integrating] DNA plasmid comprising a polynucleotide which encodes interferon alpha [encoding a cytokine,] or an active fragment thereof, through operable association with a promoter, [and] wherein said DNA plasmid is administered free from *ex vivo* cells or *ex vivo* cellular material; [such that said cytokine] and wherein said interferon alpha is delivered to a tumor, or metastases thereof, in a therapeutically effective amount.

The following claim 69 was substituted for the pending claim 69:

69. (Once Amended) The method of 66, wherein said tumor disseminates in [a body] said peritoneal cavity.

The following claim 71 was substituted for the pending claim 71:

71. (Once Amended) The method of claim 66, wherein said [construct] DNA plasmid is free from association with transfection-facilitating proteins, viral particles, and calcium phosphate precipitating agents.

The following claim 72 was substituted for the pending claim 72:

72. (Once Amended) The method of claim 66, wherein said [construct] DNA plasmid is administered as a complex [of said construct and] with one or more cationic lipids.

The following claim 73 was substituted for the pending claim 73:

73. (Once Amended) The method of claim 72, wherein said complex further [comprising] comprises one or more neutral lipids.

The following claim 74 was substituted for the pending claim 74:

74. The method of claim 73, wherein said [polynucleotide construct] DNA plasmid is complexed with (±)-N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-1-propaniminium bromide and 1,2-dioleoyl-glycero-3-phosphoethanolamine.

The following claim 78 was substituted for the pending claim 78:

78. (Once Amended) A method of [selectively] transfecting malignant cells in [a body cavity of] a mammal, comprising:

administering into [a body] the peritoneal cavity of said mammal a [non-infectious, non-integrating] DNA plasmid [encoding a molecule] comprising a polynucleotide encoding interferon alpha, or an active fragment thereof, through operable association with a promoter, [and] wherein said DNA plasmid is administered free from *ex vivo* cells or *ex vivo* cellular material; [such that said molecule] and wherein said plasmid is delivered [substantially] to and expressed in malignant cells within said [body] peritoneal cavity.

The following claim 83 was substituted for the pending claim 83:

83. (Once Amended) The method of claim 78, wherein said [construct] DNA plasmid is free from association with transfection-facilitating proteins, viral particles, and calcium phosphate precipitating agents.

The following claim 84 was substituted for the pending claim 84:

84. (Once Amended) The method of claim 78, wherein said [construct] DNA plasmid The method of claim 78, wherein said [construct] DNA plasmid is administered as a complex [of said construct and] with one or more cationic lipids.

The following claim 86 was substituted for the pending claim 86:

86. (Once Amended) The method of claim 85, wherein said [polynucleotide construct] DNA plasmid is complexed with (±)-N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-1-propaniminium bromide and 1,2-dioleoyl-glycero-3-phosphoethanolamine.